REMARKS

The final Office Action mailed October 19, 2005, has been carefully studied. Upon entry of the present amendment, the claims in the application will be claims 1-12, 14 and 15 only. These claims define novel and unobvious subject matter under Sections 102 and 103, and should be allowed. Applicant accordingly respectfully requests favorable reconsideration, entry of the amendments presented above[1], and allowance.

The double patenting rejection mentioned in paragraphs 3-5 of the Final Action has been withdrawn as indicated in the bottom paragraph on page 4 of the Final Action, so applicant need not further address such provisional double patenting rejection.

Claims 1, 2, 5 and 7 have been rejected as obvious under Section 103 from Barquinero in view of Foster, both previously cited and applied. This rejection is again respectfully traversed for the reasons set forth in the preceding Reply to the earlier Office Action.

However, applicant need not further address this rejection with respect to claims 1 and 5-7 in view of the

[1] As applicant is filing herewith an RCE, such amendments should be entered as a matter of right, even though the amendments to claim 2 present new issues.

proposed amendment to claim 1 made above which incorporates features from dependent claims which have not been so rejected.

With respect to claim 2, it is proposed to be amended above based on the disclosure at page 6, lines 10-14 of applicant's specification. The arguments of the preceding Reply are fully applicable, and the features proposed to be added to claim 2 provide additional distinguishing features over any possible combination of Braquinero in view of Foster. Claim 2, as proposed above to be amended, requires the claimed kit to comprise -

- a means for testing for the presence and/or concentration of antibodies to PAF and/or antibodies to an antigen that binds to antibodies to PAF; and
- a means for testing for the concentration of at least one further diagnostic indicator of vascular dysfunction, vascular disease and/or spontaneous abortion, selected from the group consisting of cholesterol, blood lipids or p-hydroxyphenylaldehydelysine.

As discussed on page 6 of the present application (paragraph [0013]), an improved accuracy of diagnosis can be achieved by a combined approach of testing for the defined antibodies and

also testing for the concentration of one or more of the additionally defined diagnostic indicators.

None of the cited prior art suggest that a kit should be produced comprising *both* of the above-defined means for testing; certainly there is no suggestion in the prior art that a kit comprising *both* of the above-defined means for testing would allow the user of such a kit to apply a diagnostic method that has an improved ability to accurately diagnose early vascular dysfunction, vascular disease and/or spontaneous abortion.

The cited prior art would not have motivated the person of ordinary skill in the art to combine, in a single kit, both of the above-defined means for testing. Accordingly, a kit as defined by Claim 2 and its dependent claims, which comprises both of the above-defined means for testing, would clearly have been non-obvious.

Withdrawal of the rejection is in order and is respectfully requested.

Claims 3, 4, 8 and 10 again have been rejected under Section 103 as obvious from Barquinero in view of Foster and further in view of Ostermann. This rejection is again respectfully traversed, and again for the reasons set forth in the preceding Reply.

In addition to the reasons set forth in the preceding Reply, which reasons are still valid as pointed out further near the end of this Reply, applicant respectfully notes that all of these claims depend from and incorporate the subject matter of claim 1 which, in its present form, would not be met even if the proposed combination were obvious. In other words, claims which contained the features added to claim 1 have not been included in this rejection, and consequently this rejection need not be further addressed.

Withdrawal of the rejection is in order and is respectfully requested.

Claims 11-18 have been rejected again as obvious under Section 103 from Barquinero in view Foster and further in view of Karasawa. This rejection is again respectfully traversed for reasons as set forth in the preceding Reply and as further explained below.

As noted above, the position of the PTO is that the combination of Barquinero and Foster makes it obvious to produce a kit comprising a means for testing for antibodies that bind to PAF ("aPAF"), although this combination of documents is not considered in the Final Action to make it obvious to determine the presence of antibodies to one or more of phosphocholine, phosphorylcholine, phosphatidylcholine, and/or lysophosphatidyl-choline (i.e. Claims 11-19). However,

the rejection indicates that Claims 11-19 would have been obvious in view of the combination of Barquinero and Foster, when further combined with Karasawa.

In this regard, the rejection states that Karasawa discloses systems to detect antibodies to PAF. With respect, applicant submits that the PTO has confused the issue of detection of antigen (in this case PAF) with the detection of antibody (in this case, aPAF). Contrary to the rejection, Karasawa absolutely discloses a system for the detection of PAF, *not for the detection of aPAF*. Specifically, Karasawa discloses the development of the radioimmunoassay method to measure levels of PAF (not *antibodies to* PAF) in a biological sample.

The test of Karasawa uses serum obtained from a PAF-immunised rabbit. This serum contains a mixture of different antibodies that contains, amongst others, antibodies to PAF. Karasawa teaches that the serum is used to detect PAF in a sample. Page 1127, second column, first paragraph of the "results" section, reports that "*For the radioimmunoassay, we used antiserum collected after the fourth injection*".

The radioimmunoassay of Karasawa involves measuring the level of PAF in a sample by measuring the ability of any PAF in that sample to compete with radio-labelled PAF to bind to antibodies in the rabbit antiserum. This method does not

measure the levels of the antibody to PAF in the collected antiserum (i.e. there is no measurement of aPAF). On the contrary, the antiserum that is collected is used by Karasawa as a tool in the quantification of PAF in a sample of choice.

Since the collected antiserum used in the radioimmunoassay of Karasawa contained a *mixture* of antibodies from the rabbit, some (in fact most) of the antibodies in the sample would not be specific to PAF. Accordingly, competitive inhibition of binding of the radio-labelled PAF to the antiserum, by compounds in the biological sample being tested, could potentially be due to the presence of an antibody in the antiserum that has a non-specific binding affinity both for PAF and also other molecules in the biological sample tested, and those other molecules being able to compete with, and inhibit the binding of, radio-labelled PAF to this non-specific antibody in the antiserum. In that case, it should be clear that the radioimmunoassay could not be used to reliably quantify the level of PAF in a sample.

Because of this potential problem, Karasawa *et al* wanted to check that they were observing a specific binding of PAF in the competitive radioimmunoassay. To do this, they compared the binding of the antiserum to other PAF-like molecules. Page 1128, second column, lines 2-8 reports that:

"Cross-reactivity studies of the antiserum revealed a high specificity for PAF. Choline-containing phospholipids such as lysoPAF, lecithin or lysoPC did not cross-react with PAF antiserum (Table 1)" (emphasis added).

In other words, Karasawa *et al* satisfied themselves that the antiserum sample that they obtained could be reliably used to measure the level of PAF in a sample, because the antiserum did not contain any antibodies that would non-specifically bind both PAF and other PAF-like molecules.

Likewise, in Barquinero, page 57, left hand column, the authors reported that anti-PAF antibodies that had been affinity purified using PAF as a ligand did not cross react with phosphatidylcholine and other phospholipids (see section entitled *"Affinity purified anti-PAF"*). The section that follows (entitled *"Inhibition studies"*) reports that the binding of PAF to affinity-purified IgM anti-PAF antibodies could be inhibited by the presence of phosphatidylcholine, which suggests that some anti-PAF antibodies can also bind to phosphatidylcholine, but that section also reports that *"PAF produced the highest inhibition"* which tells the reader that the best way to capture such antibodies is to use PAF as an affinity ligand.

Therefore, the teachings of both Karasawa and Barquinero is that, generally, anti-PAF antibodies do not bind to other PAF-like molecules and, where they do (such as in the case of the binding of IgM anti-PAF antibodies to phosphatidylcholine, as discussed in Barquinero), then such antibodies still bind more strongly to PAF itself.

Accordingly, in light of the teaching of Barquinero, either alone, or in combination with the teaching of Karasawa, the person of ordinary skill in the art would have been motivated to use PAF **alone** to determine the presence of anti-PAF antibodies in the sample of patient.

There is no motivation in either of Barquinero or Karasawa (each alone or both together) to test a serum sample from a patient for the presence of antibodies other than anti-PAF antibodies (because there is no indication that such antibodies exist, much less that they have any clinical significance). Accordingly, in light of the teaching of Barquinero, alone or in combination with Karasawa, the skilled person would only be motivated to determine the presence of anti-PAF antibodies in a sample from a patient and, as discussed above, the teaching of Barquinero is that, to the extent that one wishes to determine the presence of anti-PAF antibodies, then one should use PAF as a ligand to capture such antibodies.

Therefore, it would not have been obvious, in light of these prior art documents even when considered together, to use any of phosphocholine, phosphorylcholine or lysophosphatidylcholine to determine the levels, in a patient's sample, of antibodies that bind to these compounds.

Foster adds nothing to the teaching of either Barquinero or Karasawa in respect of the issue of using to any of phosphocholine, phosphorylcholine or lysophosphatidyl-choline to determine the levels, in a patient's sample, of antibodies that bind to these compounds.

Furthermore, phosphocholine, phosphorylcholine and lysophosphatidylcholine are smaller, more simple molecules than PAF, and accordingly comprise fewer epitopes than PAF. As a result, the use of phosphocholine, phosphorylcholine and/or lysophosphatidylcholine as a ligand provides the user with the ability to bind a more specific group of antibodies. This advantage was not appreciated in the cited art.

In summary, the cited prior art teaches the person skilled in the art to continue to use PAF to detect anti-PAF antibodies (i.e. aPAF) and so the references teach away from the present invention and fail to appreciate the advantages provided in the present invention.

Therefore, Claim 1 and its dependent claims are would not have been obvious from the combined teachings

Barquinero, Foster and Karasawa, even if obviously combinable, the obviousness of such a combination being respectfully denied.

Claim 19 has been rejected as obvious from Barquinero in view of Foster, Ostermann and Karasawa. This rejection is respectfully traversed, and again for the reasons of record appearing at page 19 of the previous Reply.

The arguments appearing above with respect to the rejection of claims 11-18 apply equally to the rejection of claim 19, it being noted that Ostermann adds nothing with respect to the deficiencies of the combination of Barquinero in view of Foster and further in view of Karasawa for the reasons pointed out above.

Withdrawal of the rejection is in order and is respectfully requested.

Applicant does not wish to leave unanswered the part of the Final Action under the heading "Response to Arguments" commencing at page 10. In this regard, applicant must state, although with respect, that the PTO cannot brush aside an applicant's arguments simply by stating that the references were discussed individually. Of course they were and must be discussed individually! They must be discussed individually to make any sense of the references. But the implication of

the criticism is that they were **only** discussed individually, and this is absolutely incorrect. In this regard, applicant briefly notes the Remarks of the preceding Reply commencing with the bottom paragraph on page 15 and extending through the bottom paragraph on page 16, which deal with the first rejection. Applicant's Reply to the other rejection similarly deals with the proposed combinations. See for example the second paragraph on page 19 of the preceding Reply.

Respectfully, applicant's arguments, including those arguments pointing the non-obviousness of the combination and the fact that the references even if combined would not reach the invention, deserve a complete answer or rebutal, or the claims should be allowed.

As regards the points raised in the bottom paragraph on page 10 of the Official Action, applicant respectfully points out that the kit of the present invention is for the purpose of diagnosis, and so of course there is no requirement for the patient to be free from vascular disease prior to testing. The purpose of the kit is to determine, when used on a patient, whether that patient suffers a condition of early vascular dysfunction, vascular disease, and/or spontaneous abortion. The invention is to be considered "as a whole"; this includes features which are implicit in the claims and inherent in the claimed subject matter.

As regards the top paragraph on page 11 of the Final Action, it has been pointed out above that the references provide no motivation for what applicant has done. The rejections improperly extrapolate the teachings of the references to something that the references do not teach.

As regards the second paragraph on page 11 of the Final Action, applicant has fully addressed this matter above. It does not matter if the claimed language is open or closed. The references do not teach the claimed subject matter.

As regards the bottom paragraph on page 11, this matter has also been fully addressed above. Again, the references simply do not teach or suggest the claimed subject matter. There is no motivation to change what they teach to something that they do not teach.

As regards the top two paragraphs on page 12 of the Final Action, again these points have been fully addressed above, and again the references, either singly or in any possible combination, simply do not lead one of ordinary skill in the art to or even towards the present invention. The teachings of the references have been twisted like a nose of wax.

The court stated in *In re Shuman* and *Meinhardt*, 150 USPQ 54 (1966) at page 57:

> References are evaluated by ascertaining the facts fairly disclosed therein <u>as a</u>

> whole. It is impermissible to first ascertain factually what appellants did and then view the prior are in such a manner as to select from the random facts of that are only those which may be modified and then utilized to reconstruct appellants' invention from such prior art. (emphasis added)

As regards the bottom paragraph on page 12 of the Final Action, the issue is not whether a reference may be bodily incorporated into another. The references have contrary teachings, and the only thing that makes their combination even remotely possible is applicant's own disclosure, something that was not available to the person of ordinary skill in the art at the time the present invention was made.

As regards the two paragraphs on page 13 of the Final Action, these points have also been fully addressed above. The references do not lead to or toward the present invention, and the PTO improperly brushes aside invention as "routine adjustment" without any evidence whatsoever in support of such a position, clearly contrary to the law. The PTO has not met its burden under MPEP 2143, and does not meet the basic requirements of *Ex parte Levengood*, 28 USPQ 1300, 1301-1302 (BPAI 1993).

The prior art documents of record and not relied upon by the PTO have been noted, along with the implication

that such documents are deemed by the PTO to be insufficiently material to warrant their application against any of applicant's claims.

Applicant believes that all issues raised in the Office Action have been addressed above in a manner favorable to allowance of the present application. Accordingly, applicant respectfully requests favorable reconsideration and early formal allowance.

Respectfully submitted,

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